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### Abstract

**Objective** To investigate the usefulness of measuring plasma concentrations of B type natriuretic peptide in the diagnosis of left ventricular systolic dysfunction in an unselected group of elderly people.

**Design** Observational study.

**Setting** General practice with four centres in Poole, Dorset.

**Participants** 155 elderly patients aged 70 to 84 years.

**Main outcome measures** Diagnostic characteristics of plasma B type natriuretic peptide measured by radioimmunoassay as a test for left ventricular systolic dysfunction assessed by echocardiography.

**Results** The median plasma concentration of B type natriuretic peptide was 39.3 pmol/l in patients with left ventricular systolic dysfunction and 15.8 pmol/l in those with normal function. The proportional area under the receiver operator curve was 0.85. At a cut-off point of 18.7 pmol/l the test sensitivity was 92% and the predictive value 18%.

**Conclusions** Plasma concentration of B type natriuretic peptide could be used effectively as an initial test in a community screening programme and, possibly, using a low cut-off point, as a means of ruling out left ventricular systolic dysfunction. It is, however, not a good test to "rule in" the diagnosis, and access to echocardiography remains essential for general practitioners to diagnose heart failure early.

### Introduction

Diagnosis in general practice is difficult, and the clinical diagnosis of left ventricular dysfunction is no exception. It is known that morbidity and mortality can be reduced by treating patients with ventricular dysfunction with angiotensin converting enzyme inhibitors. There is, however, no simple and reliable clinical method of identifying such patients. The classic signs of raised jugular venous pressure and fine basal crepitations become evident at the later stages of heart failure when there is severe dysfunction. The clinical correlates of less severe dysfunction are of lesser diagnostic value as no identified clinical symptom or sign is both sensitive and specific.<sup>1</sup> Inappropriate treatment of ventricular dysfunction in primary care (due to both underdiagnosis and overdiagnosis) is leading to unnecessary morbidity and mortality.<sup>2</sup>

Recent interest has been shown in the utility of assays of natriuretic peptide for screening and diagnosing heart failure. The concept of a biochemical test for heart failure is appealing to general practitioners, who are often faced with breathless and fatigued patients. Several natriuretic peptides have been considered for this role. C terminal and N terminal atrial natriuretic peptides are secreted in response to the stretch that occurs with increased left atrial pressure associated with heart failure. The natriuretic peptide that is thought to have most diagnostic value in this context is the brain or B type (so called because it was first identified in the porcine brain in 1988<sup>3</sup>). The main source of this peptide in humans is the cardiac ventricle, and the potential utility of plasma concentrations as a diagnostic indicator of early ventricular failure has been reported.<sup>4</sup>

Measurement of the plasma concentration of B type natriuretic peptide might be diagnostically useful in primary care. Cowie et al reported a likelihood ratio of 6.1 (sensitivity 97%, specificity 84%, cut-off point 22.2 pmol/l) for the diagnosis of heart failure in a sample of 106 patients with symptoms who were referred by general practitioners to a rapid access outpatient clinic.<sup>5</sup> McDonagh et al reported a similar likelihood ratio of 5.8 (sensitivity 76%, specificity 87%, cut-off point 5.1 pmol/l) for the diagnosis of left ventricular systolic dysfunction in an unselected group of 1653 patients aged 25-74 years who had participated in the monitoring trends and determinants in cardiovascular disease project.<sup>6</sup>

There is no doubt about the potential importance of these findings. Clinical diagnosis of mild and moderate heart failure is difficult and imprecise in general practice. Hospital based echocardiography services are often stretched, facilities for echocardiography are not widely available in the community, and current technology is not easily mobile. Neither of these studies, however, included many elderly patients, on whom the test is most likely to be used in general practice. It has been argued that impaired renal function and other comorbidity in elderly patients leads to raised concentrations of blood B type natriuretic peptide, thus reducing the predictive value of the test in routine clinical use.<sup>7</sup> We aimed to investigate the usefulness of B type natriuretic peptide in the identification of left ventricular systolic dysfunction in an unselected group of elderly patients.

## Participants and methods

We conducted our study in the context of a prevalence study of left ventricular systolic dysfunction in elderly patients. We screened a random sample of 817 elderly patients aged 70-84 years from general practice (77.4% of 1056 eligible patients).<sup>1</sup> The mean age of the patients was 75.6 years (SD 3.7 years). Diagnosis was based on echocardiographic assessment of global and regional ventricular function, including measurement of left ventricular ejection fraction. A random sub-sample of 160 consecutive patients was also asked to undergo venepuncture. Five samples were unsuitable for analysis; the results presented are therefore based on 155 patients.

### Sample collection, storage, and assay

A 10 ml sample of venous blood was taken from the study participants. The sample was put into tubes containing edetic acid as an anticoagulant and 0.5 ml trasyol to prevent breakdown of natriuretic peptide. Within half an hour the sample was spun in a refrigerated centrifuge (4°C) at 3000 rpm for 15 minutes. The separated plasma was divided into two aliquots and stored at -20°C until it was transferred to storage at -70°C at the end of each day or within 24 hours. The plasma was applied to C8 solid extraction columns, which were pretreated with 4 ml methanol, 4 ml distilled water, and 4 ml 1% trifluoroacetic acid. The columns were then washed with 9 ml of 1% trifluoroacetic acid and the sample eluted with 4 ml of 95% methanol and 1% trifluoroacetic acid. The eluted peptides were dried and redissolved in buffer for analysis using standard commercial kits (Peninsular Laboratories Europe, St Helen's, Merseyside). The interassay and intra-assay coefficients of variation were 14.8% and 9.9% respectively. The laboratory reference range for B type natriuretic peptide is 2.34-4.43 pmol/l.

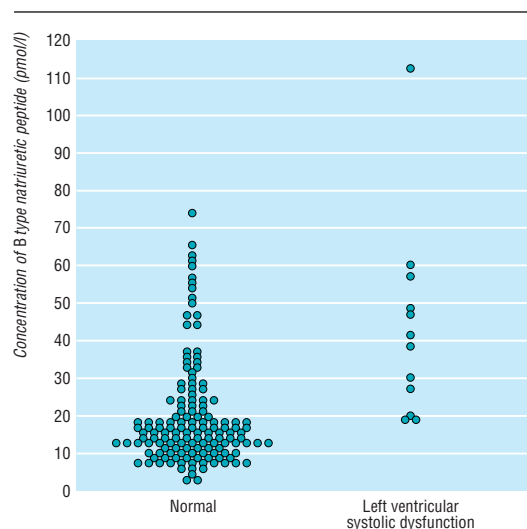
### Statistical analysis

A receiver operator characteristic curve was drawn, and we analysed B type natriuretic peptide as a predictor of left ventricular systolic dysfunction with SPSS (release 9.0). We chose three cut-off points of B type natriuretic peptide to achieve sensitivity values of at least 90%, 80%, and 70%. For each resulting sensitivity we calculated specificity and both positive and negative predictive values. Likelihood ratios for positive and negative test results are also presented with exact 95% confidence intervals, calculated in StatXact (release 4).

## Results

Figure 1 shows the distribution of plasma concentrations of B type natriuretic peptide in normal elderly people and in those with left ventricular systolic dysfunction confirmed by echocardiography. The median concentration of B type natriuretic peptide was 39.3 pmol/l in patients with ventricular dysfunction and 15.8 pmol/l in those with normal function.

Figure 2 and the table show the operating characteristics of B type natriuretic peptide as a diagnostic test in elderly patients. We show the trade-off between true positive and false positive rates by presenting the data as a traditional receiver

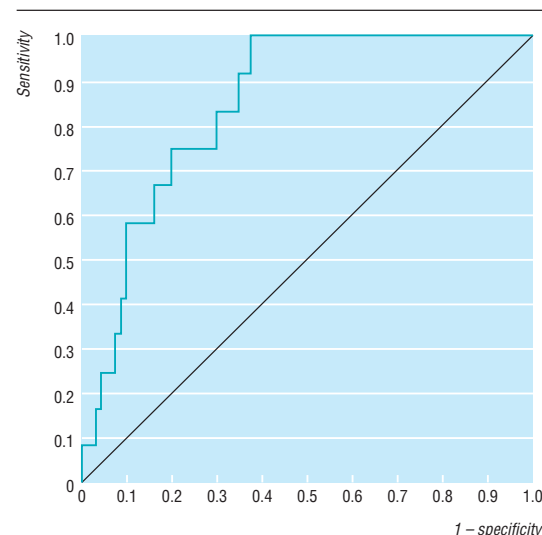


**Fig 1** Distribution of plasma concentrations of B type natriuretic peptide in normal elderly people and in those with left ventricular systolic dysfunction confirmed by echocardiography

operator curve (fig 2). The proportional area under the curve is 0.85. The table shows the predictive values and likelihood ratios at specific cut-off points, chosen to approximate to sensitivities of 90%, 80%, and 70%. At the lowest cut-off point shown (18.7 pmol/l, sensitivity 91.7%) the predictive value achieved was 18%. Setting the cut-off point to achieve a sensitivity of 100% would lower the predictive value further.

## Discussion

The measurement of plasma concentrations of B type natriuretic peptide in elderly patients in general practice could be an invaluable aid in the diagnosis of ventricular dysfunction. One of our main concerns was whether B type natriuretic peptide would maintain its diagnostic value in elderly patients with multiple disease in whom it is most likely to be used in primary



**Fig 2** Receiver operator characteristic curve for plasma B type natriuretic peptide

Operating characteristics of different cut-off points for plasma concentrations of B type natriuretic peptide. Values are percentages (numbers) of patients unless stated otherwise

Characteristics	B type natriuretic peptide (pmol/l)		
	≥18.7	≥19.8	≥26.7
Sensitivity	92 (11/12)	83 (10/12)	75 (9/12)
Specificity	65 (93/143)	70 (100/143)	80 (115/143)
Positive predictive value	18 (11/61)	19 (10/53)	24 (9/37)
Negative predictive value	99 (93/94)	98 (100/102)	98 (115/118)
Likelihood ratio* (95% CI)	2.6 (1.4 to 4.1)	2.8 (1.3 to 4.7)	3.8 (1.6 to 7.6)
Likelihood ratio† (95% CI)	0.13 (0.00 to 0.55)	0.24 (0.11 to 0.69)	0.31 (0.03 to 0.72)

\*Positive test result.

†Negative test result.

care. There are good theoretical grounds for suspecting that B type natriuretic peptide might be increased for reasons other than ventricular dysfunction in such patients. The test may not perform as well in elderly as in young patients, but it still works.

Measuring plasma concentrations of B type natriuretic peptide has two potential diagnostic uses in a community setting—for screening populations for the detection of previously unrecognised heart failure and as an aid to clinical decision making about a patient with symptoms. The value of the test is not necessarily the same for each use. The limitation of plasma B type natriuretic peptide in a screening programme for elderly patients is its low predictive value. For example, to identify nine out of 10 patients with ventricular dysfunction requires a cut-off point at which only one in five patients testing positive has the condition. B type natriuretic peptide would therefore have to be used as a first stage screening examination followed by second stage screening with echocardiography in a more specialised setting.

An example of the value of plasma concentrations of B type natriuretic peptide as a diagnostic test in patients with symptoms in general practice would be an elderly patient with breathlessness on walking (pre-test probability of ventricular dysfunction about 15%).<sup>1</sup> The test would not be helpful in confirming a diagno-

sis of ventricular dysfunction in this situation—even using the cut-off point that maximises the likelihood ratio of a positive test (26.7 pmol/l, likelihood ratio 3.8), the post-test probability would still be under 40%. This probability is too low to eliminate the need for further investigation. Conversely, the test may be useful for ruling out left ventricular dysfunction. If the test was negative at a cut-off point of 18.7 pmol/l in the same patient, the probability in a post-test would be less than 2%. Moreover, it might be possible to choose an even lower cut-off point at which left ventricular dysfunction could be effectively ruled out, although our sample size is insufficient to estimate this point with any precision.

One important point that emerged during the study is that measuring plasma concentrations of B type natriuretic peptide is feasible in general practice. Although the blood samples in this study were processed rapidly, being centrifuged on site before freezing to  $-20^{\circ}\text{C}$  within 30 minutes and later being transferred to storage at  $-70^{\circ}\text{C}$ , it has now been shown that this is unnecessary. B type natriuretic peptide is stable in routine tubes containing ethylenediamine tetraacetic acid and stored at room temperature for at least six hours—sufficient time for the sample to be transported from general practice to the hospital laboratory without the need for prior spinning or freezing.<sup>8</sup>

B type natriuretic peptide has diagnostic value in elderly patients in routine general practice. It could be used effectively as an initial test in a community screening programme and, possibly, using a low cut-off point, as a means of ruling out a diagnosis of left ventricular systolic dysfunction. It is, however, not a good test to “rule in” the diagnosis. The immediate implication for NHS provision is that even if a B type natriuretic peptide blood test is done, access to echocardiography remains essential for general practitioners to make an early diagnosis of heart failure.

This report is based on an echocardiographic screening study conducted in the Adam practice, Dorset, under Dr G S Liddiard. Helen Raphael provided practical support.

Contributors: HS initiated and developed the protocol and coordinated the study. All authors contributed to protocol refinement, discussed and interpreted the data, and revised the paper. AS provided expertise in biochemical assays, IS reviewed the echocardiograms, and RMP performed the statistical analysis. DM edited the paper. HS will act as guarantor for the paper.

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Competing interests: None declared.

### What is already known on this topic

No simple or reliable method is available for the clinical diagnosis of early left ventricular systolic dysfunction in general practice

Measurement of plasma concentrations of natriuretic peptides, for example the B type, may be of diagnostic value, but previous studies of diagnostic utility have focused on young patients whereas the burden of disease is among elderly people

### What this study adds

The test performs less well in elderly than young patients, but it still works

In elderly people measurement of plasma concentrations of B type natriuretic peptide may be helpful as an initial community screening test and to rule out the diagnosis of early left ventricular systolic dysfunction in patients with symptoms in general practice

Diagnostic confirmation of early left ventricular systolic dysfunction in patients with symptoms or in those screened in general practice still requires access to echocardiography

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